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Mathematical Model of the use of Caffeine as a countermeasure to the deterioration of psychomotor vigilance during sustained operations & jet lag.

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13. ABSTRACT ***(Maximum 200 Words)***

This project seeks a quantitative description of the dynamics of homeostatic and circadian influences on human sleep/wake patterns, cognitive and psychomotor performance. Equations have been developed by R. Kronauer and M. Jewett for the circadian/homeostatic interaction, as well as for the photic entrainment of the circadian pacemaker. [See Journal of Biological Rhythms, December 1999, Vol. 14, Issue 6 for a complete statement of these models.] Data from human forced desynchrony trials were used to test and evaluate the model, and to estimate parameters. Predictions were examined for measures of cognitive throughput as well as for measures of subjectively-assessed fatigue. Effects of caffeine were studied. Software incorporating the mathematical model and findings from several empirical studies was developed to simulate and predict human performance in a variety of sleep/wake routines.

14. SUBJECT TERMS	15. NUMBER OF PAGES
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Final Progress Report

1. Cover Sheet

Principal Investigator:	Megan E. Jewett, Ph.D.
Affiliation:	Brigham and Women's Hospital 75 Frances Street Boston MA 02115
Title:	"Mathematical Models of the Use of Caffeine as a Countermeasure Deterioration of Neurobehavioral Functioning During Circadian Misalignment and Sleep Deprivation"
Grant Number:	F496200110004

2. Objectives

As included in the original application for the Army "Young Investigator Program":

1) To refine mathematical models that accurately predict the homeostatic (sleep/wake) and circadian regulation of human subjective alertness, cognitive throughput, psychomotor vigilance, and short-term memory during sleep deprivation and circadian misalignment.

2) To validate these models using data from sleep deprivation studies that were initiated across the full circadian cycle.

3) To incorporate into these models the effects of a frequent low-dose caffeine regimen on human alertness and performance in order to determine the appropriate use of caffeine as a countermeasure to the impairment caused by sleep deprivation and circadian misalignment.

3. Status of effort

Specific aims 1 and 2 are complete. Results from the refined and validated models were presented in manuscripts and at meetings (see listing below). Work on specific aim3 is in progress. We have completed preparing the data for unblinding (caffeine/placebo) and then incorporation into the model. We will continue to work on this project, even though this grant has ended.

4. Accomplishments/New Findings

Please see the published manuscripts, reports, and presentations listed below.

In addition, the software for use of the refined and validated model is available at: http://dsm.bwh.harvard.edu/bmu/cpss. This software has been distributed to 134 sites. More information is contained in the Transitions section, below.

5. Personnel Supported

Principal Investigator: Megan E. Jewett Ph.D.

6. Publications

Peer-reviewed publications and abstracts submitted and/or accepted during the grant period:

1) Jewett ME, Wyatt JK, Ritz-De Cecco A, Khalsa SB, Dijk, D-J, Czeisler CA. Time course of sleep inertia dissipation in human performance and alertness. J. Sleep Res. 1999;8:1-8.

2) Jewett ME, Dijk D-J, Kronauer RE, Dinges DF. Dose-response relationship between sleep duration and human psychomotor vigilance and subjective alertness. Sleep 1999;22:171-179.

3) Khalsa SBS, Jewett ME, Duffy JF, Czeisler CA. The timing of the human circadian clock is accurately represented by the core body temperature rhythm following phase shifts to a 3 cycle light stimulus near the critical zone. J. Biol. Rhythms 2000;15:524-530.

4) Wright Jr. KP, Kronauer RE, Jewett ME, Ronda JM, Klerman EB, Czeisler CA. Human circadian entrainment to the 24 hr day in a dim light-dark cycle. Sleep Res Online 1999; 2 (Suppl. 1): 739.

5) Jewett ME, Dijk D-J, Kronauer RE, Czeisler CA. Sigmoidal decline of homeostatic component in subjective alertness and cognitive throughput. Sleep 1999;22:S94-S95.

6) Jewett ME, Wyatt JK, Ritz-De Cecco A, Dijk D-J, Khalsa SB, Czeisler CA. Cognitive throughput and subjective alertness after awakening: investigation of sleep inertia with respect to three different circadian phases. Sleep 1999;22:S88-S89.

7) Czeisler CA, Wright KP Jr., Rimmer DW, Jewett M, Kronauer RE. Evaluation of intermittent bright light exposure as a space flight countermeasure. NASA First Biennial Space Biomedical Investigators' Workshop, 1999: 341.

8) Wright KP Jr., Klerman, EB, Jewett M, Kronauer RE, Czeisler CA. Circadian Entrainment, sleep-wake regulation and neurobehavioral performance under the simulated lighting conditions of long-duration space missions. NASA First Biennial Space Biomedical Investigators' Workshop, 1999: Supplement 51-52.

9) Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to shifts of the sleep/wake schedule in humans. Internat. Cong. on Chronobiology, 8/21-9/1/99, Washington, D.C.

10) Ritz-De Cecco A, Jewett ME, Wyatt JK, Kronauer RE, Czeisler CA, Dijk D-J. Plasma melatonin rhythm in humans during a 20-h forced desynchrony protocol. World Federation of Sleep Research Societies conference, Dresden, Germany. October; 1999.

11) Benke KS, Jewett ME, Kalsa SBS, Czeisler CA. Hourly and 30-minute sampling: similar phase estimates for plasma melatonin. Abstracts, Northeastern Sleep Society Mtg., Worcester, MA; 2000.

12) Couzin-Wood C, Hughes RJ, Jewett ME, Ritz-De Cecco A, Khalsa SBS, Klerman EB, Czeisler CA. Low and high melatonin producers display similar nocturnal melatonin profiles. Abstracts, 13th mtg, Australasian Sleep Association; 2000; 19.

13) Jewett ME, Khalsa SBS, Klerman EB, Duffy JF, Rimmer DW, Kronauer RE, Czeisler CA. 3-cycle bright light stimulus induces type 0 resetting in human melatonin rhythm. Abstracts, 7th mtg, Society for Research on Biological Rhythms; 2000;134.

14) Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in humans. Abstracts, 7th mtg, Society for Research on Biological Rhythms; 2000;12.

15) Benke KS, Jewett ME, Kalsa SBS, Czeisler CA. Decreased sampling rates may provide acceptable melatonin phase, duration and amplitude estimates, depending on the precision required. Abstracts, 7th mtg, Society for Research on Biological Rhythms; 2000;127.

16) Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single pulses of bright light in humans. Sleep, 2000; 23: A22-A23.

17) Benke KS, Jewett ME, Kalsa SBS, Czeisler CA. Hourly and 30-minute sampling: similar phase, duration and amplitude estimates for plasma melatonin. Sleep, 2000; 23: A374-A375.

18) Jewett, ME, Wright, KP, Duffy, JF, Rodriguez, DM, Czeisler, CA. (2001) Practice Effects Observed Over a Month-Long 28-Hour Forced Desynchrony Protocol in a Cognitive Throughput Task Are Well Described by a Saturating Exponential Function.: Sleep, 2001; 24 (Suppl.):A4-A5.

19) Brown EL, Barger LK, May CD, Jewett ME. A transformation function can equate readings of wrist-worn light measuring devices to those of hand-held light monitors. Sleep, 2001; 24:A102.

20) Dean II, DA, Jewett MR, Circadian Performance Simulation Software (CPSS) provides a tool for validation of circadian and neurobehavioral mathematical models, Sleep, 2001; 24:A103-A104.

21) Ritz-De Cecco A, Jewett ME, Duffy JF, Shanahan TL, Czeisler CA. Assessment of phase shift of melatonin rhythm to a single bright light stimulus is confounded by masking effects of scheduled sleep:wake and/or dim light:dark cycles. Sleep, 2001; 24: A85.

22) Rodriguez, DM, Oyung, RL, Barger, LK, Mallis, MM, Jewett, ME. Flight Deck Light Exposure During Long-Haul Trips Between the United States and Japan. Sleep, 2002; 25: A420.

23) Gray AR, Dean, DA, Horowitz TS, Barger LK, Jewett ME. With limited input data, Kronauer's light model makes accurate circadian phase predictions on average, but makes large errors in some individual predictions. Sleep, 2002; 25: A422.

24) Dean II, DA, Jewett MR, Effects of light pulse duration and intensity in model simulations of human phase response curve, Sleep, 2002; 25: A427.

25) Indic P, Forger D B, Dean DA, Brown EN, Kronauer RE, Jewett ME. A model of human core temperature circadian rhythm with statistical and dynamic characteristics. Abstracts, 8th mtg, Society for Research on Biological Rhythms, 2002; 132.

26) Dean II, DA, Forger, DB, Indic, P, Brown, EN, Kronauer, RE, Jewett, ME, Temperature models are improved by allowing circadian amplitude to vary and replacing the second harmonic with an independent ~12-h sinusoid. Abstracts, 8th mtg, Society for Research on Biological Rhythms, 2002; 129.

27) May, C, Dean II, DA, Jewett, ME, A new mathematical definition of CBTmin improves model predictions of the effect of light on the circadian pacemaker in amplitude suppression protocols. Abstracts, 8th mtg, Society for Research on Biological Rhythms, 2002; 133.

28) Gray, AR, Dean DA, Rodriguez DR, Jewett ME, Cognitive throughput model predicts that scheduling of naps based on circadian phase improves pilot performance during ultra long-range flights. Abstracts, 8th mtg, Society for Research on Biological Rhythms, 2002; 131.

29) Ritz-De Cecco A, Jones JA, Jewett ME, Light model predicts that phase modulation during 20-h forced desynchrony protocol increases with light intensity in asymptotic manner. Abstracts, 8th mtg, Society for Research on Biological Rhythms, 2002; 56.

30) Ritz-De Cecco, Dean II, DA, Jones JA, Jewett ME, Phase modulation of DLMOn during a 20-hr forced desyncrony protocol is greater than predicted by light model, 16th Congress of the European Sleep Research Society, 2002.

31) Indic P, Dean II DA, Forger DB, St. Hilaire MA, Brown EN, Kronauer RE, Jewett ME. Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure. Bioastronautics Investigators' Workshop, 2002

Meeting Proceedings

1) Jewett ME, Forger DB, Kronauer RE. Revised limit cycle oscillator model of the human circadian pacemaker. *J. Biol. Rhythms* 1999;14:493-499.

2) Kronauer RE, Forger DB, Jewett ME. Quantifying human circadian pacemaker response to brief, extended and repeated light stimuli over the photopic range. *J. Biol. Rhythms* 1999;14:500-515.

3) Forger DB, Jewett ME, Kronauer RE. A simpler model of the human circadian pacemaker. *J. Biol. Rhythms* 1999;14:532-537.

4) Jewett ME, Kronauer RE. Interactive mathematical models of subjective alertness and cognitive throughput in humans. *J. Biol. Rhythms* 1999;14:588-597.

5) Dijk D-J, Jewett ME, Czeisler CA, Kronauer RE. Reply to technical note: nonlinear interactions between circadian and homeostatic processes: models or metrics? *J. Biol. Rhythms* 1999;14:604-605.

6) Klerman EB, Jewett ME. Commentary: Model building, quantitative testing and model comparison. *J. Biol. Rhythms* 1999;14:621-624.

7) Jewett ME, Borbély AA, Czeisler CA. Editorial: Biomathematical modeling workshop, May 18-21, 1999. *J. Biol. Rhythms* 1999;14:429-430.

8) Forger, D.B., Dean II, D.A. , Gurdziel, K., Leloup, J-C., Lee, C., von Gall, C. , Etchegaray, J-P., Kronauer, R.E., Goldbeter, A., Peskin, C. S., Jewett, M.E. and Weaver, D.R. Development and Validation of Computational Models for Mammalian Circadian Oscillators. OMICS 2003 (in press).

7. Interactions/Transitions

Participation/presentations at meetings, conferences, seminars, etc.

1) **Invited Workshop Speaker**, *Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans*, May 1999, Dedham, MA. "Quantifying human circadian pacemaker response to brief, extended and repeated light episodes over the photopic range".

2) **Invited Workshop Speaker**, *Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans*, May 1999, Dedham, MA. "Interactive mathematical models of subjective alertness and cognitive throughput in humans".

3) **Invited Workshop Speaker**, *Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans*, May 1999, Dedham, MA. "Comparison of model predictions of experimental protocols".

4) **Invited Symposium Speaker**: *Society for Research on Biological Rhythms*, May 2000, "Are circadian models medically useful?" for symposium "Construction of Circadian Models".

5) **Invited Speaker**: *National Space Biomedical Research Institute*, April 2001, Cambridge, MA. "Mathematical models of human circadian rhythms and neurobehavioral performance".

6) **Invited Speaker**: *Association of Professional Sleep Societies*, June 2001, for Discussion Group "Markers of 'sleep debt' accumulation and recovery: evidence for SWA, REM, TST?".

7) **Invited Speaker**: *Crew Alertness in Ultra Long-Range Operations,* March 2002, Paris, France. "Performance model simulations of ULR flights: results and recommendations."

8) **Invited Workshop Speaker**: *Society for Research on Biological Rhythms,* May 2002, "Models of light entrainment" for Workshop "Entrainment in humans: what does it take?"

9) **Invited Speaker**: *Fatigue and Performance Modeling Workshop,* June 2002, Seattle, WA. "Interactive neurobehavioral model."

Consultative and advisory functions to other laboratories and agencies

None, except as above under participation/presentation at meetings, conferences, seminars etc.

Transitions

Circadian Performance Simulation Software (CPSS), as described in the accomplishments/new findings section, has been distributed to 134 sites (10% industry, 30% governmental agency, 30% university related research institution, and 30% individuals). It is being used to evaluate protocols and work schedules, including evaluation of the quarantine portion of shuttle mission astronauts before launch.

8. New discoveries, inventions or patent disclosures

No inventions or patent disclosures.

9. Honors and Awards

1) **Research Merit Travel Award**, American Professional Sleep Societies, 1999.
2) **Trainee Research Excellence Award**, American Professional Sleep Societies, 1999.